

Diabetic Foot and Gangrene

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1. Introduction

“Early intervention in order to prevent potential disaster in the management of Diabetic foot is not only a great responsibility, but also a great opportunity”

Despite advances in our understanding and treatment of diabetes mellitus, diabetic foot disease still remains a terrifying problem. Diabetes is recognized as the most common cause of non-traumatic lower limb amputation in the western world, with individuals over 20 times more likely to undergo an amputation compared to the rest of the population. There is growing evidence that the vascular contribution to diabetic foot disease is greater than was previously realised. This is important because, unlike peripheral neuropathy, Peripheral Arterial Occlusive Disease (PAOD) due to atherosclerosis, is generally far more amenable to therapeutic intervention. PAOD, has been demonstrated to be a greater risk factor than neuropathy in both foot ulceration and lower limb amputation in patients with diabetes. Diabetes is associated with macrovascular and microvascular disease. The term peripheral vascular disease may be more appropriate when referring to lower limb tissue perfusion in diabetes, as this encompasses the influence of both microvascular dysfunction and PAOD.

Richards-George P. in his paper about vasculopathy on Jamaican diabetic clinic attendees showed that Doppler measurements of ankle/brachial pressure index (A/Bi) revealed that 23% of the diabetics had peripheral occlusive arterial disease (POAD) which was mostly asymptomatic. This underscores the need for regular Doppler A/Bi testing in order to improve the recognition, and treatment of POAD. Ageing is associated with both neuropathic ulcers and peripheral vascular diseases among individual with diabetes.

2. Diabetic foot

The foot of a diabetic patient has the potential risk of pathologic consequences, including ulceration, infection and/or destruction of deep tissues associated with neurologic abnormalities, varying degrees of peripheral vascular disease and/or metabolic complications of diabetes in the lower limb.

2.1 Epidemiology and problem statement of diabetic foot

The foot ulcer incidence rates range between 2% and 10% among patients with diabetes mellitus. The age adjusted annual incidence for non traumatic lower limb amputations in diabetic persons ranges from 2.1 to 13.7 per 1000 persons.¹

It is estimated that 15% of diabetic patients will experience a foot ulcer at some time over the course of their disease. People with foot problems and diabetes mellitus have 15 times the increased risk of undergoing a lower extremity amputation compared to those without diabetes². Amputation is the end result of a cascade of diabetic foot leg lesions. Twenty percent of all diabetic persons enter the hospital because of foot problems. One study in UK showed that 50% of the hospital bed occupancy of diabetic patients is caused by foot problems. Apart from the morbidity and mortality associated with diabetic foot ulcers and amputations, the economic and emotional consequences for the patient and the family can be enormous³.

2.2 Classification of the diabetic foot⁴

For practical purposes, the diabetic foot can be divided into two entities, the neuropathic foot and the ischaemic foot. However, ischaemia is nearly always associated with neuropathy, and the ischaemic foot is best called the neuroischaemic foot. The purely ischaemic foot, with no concomitant neuropathy, is rarely seen in diabetic patients.

2.2.1 The neuropathic foot

- It is a warm, well perfused foot with bounding pulses due to arteriovenous shunting and distended dorsal veins.
- Sweating is diminished, the skin may be dry and prone to fissuring
- Toes may be clawed and the foot arch raised.
- Ulceration commonly develops on the sole of the foot
- Despite the good circulation, necrosis can develop secondary to severe infection.
- It is also prone to bone and joint problems (the charcot foot).

2.2.2 The neuroischaemic foot

- It is a cool, pulseless foot with reduced perfusion and invariably has neuropathy.
- The colour of the severely ischaemic foot can be a deceptively healthy pink or red, caused by dilatation of capillaries in an attempt to improve perfusion. If severely infected, the ischaemic foot may feel deceptively warm.
- It may also be complicated by swelling, often secondary to cardiac or renal failure.
- The most frequent presentation is that of ulceration. Ischaemic ulcers are commonly seen on the margin of the foot, which includes the tips of the toes and the areas around the back of the heel, and are usually caused by trauma or by wearing unsuitable shoes
- Intermittent claudication and rest pain may be absent because of neuropathy and the distal distribution of the arterial disease of the leg.
- Even if neuropathy is present and plantar pressures are high, plantar ulceration is rare,
- It develops necrosis in the presence of infection or if tissue perfusion is critically diminished.

2.3 The natural history of the diabetic foot :

The natural history of the diabetic foot can be divided into six stages

Stage 1 : Normal - Not at risk. The patient does not have the risk factors of neuropathy, ischemia, deformity, callus and swelling rendering him/her vulnerable to foot ulcers.

Stage 2 : High risk foot - the patient has developed one or more of the risk factors for ulceration of the foot.

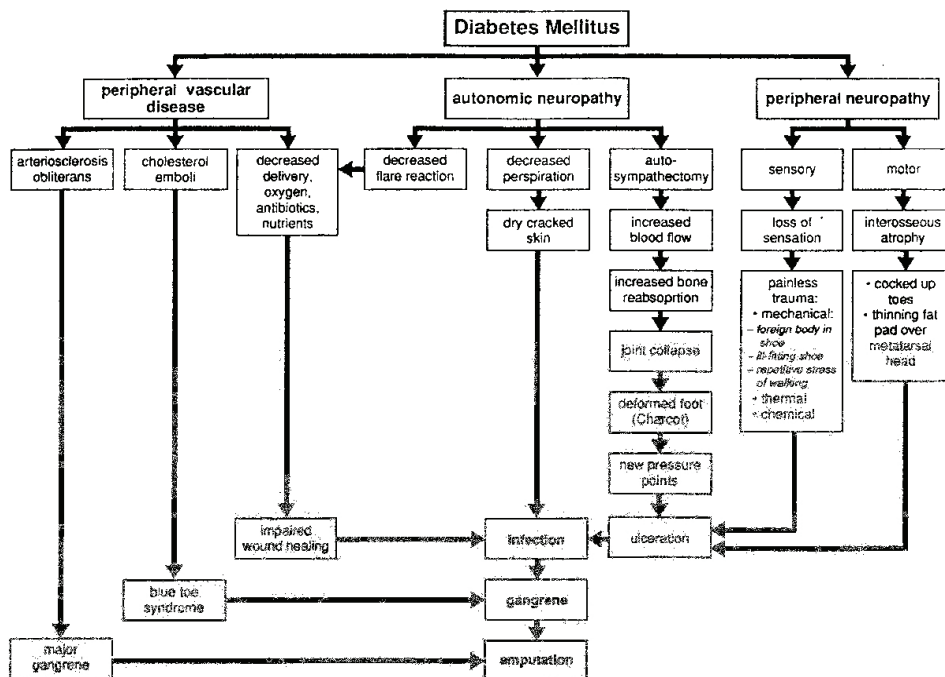
Stage 3 : Ulcerated foot – the foot has a skin breakdown. This is usually an ulcer, but because some minor injuries such as blisters, splits or grazes have a propensity to become ulcers, they are included in stage 3.

Stage 4 : Infected foot – the ulcer has developed infection with the presence of cellulitis.

Stage 5 : Necrotic foot – necrosis has supervened.

Stage 6 : Unsalvageable – The foot cannot be saved and will need a major amputation.

2.4 Pathogenesis of diabetic foot lesions⁵



3. Pathophysiology

Recent advances in molecular biology have added substantial insight into the pathophysiology of the disease and opened new avenues for treatment¹.

The predisposing factors to pathologic changes in the foot of a diabetic are

1. Metabolic factors – hyperglycemia
2. Vascular changes
3. Neuropathy
4. Infection

3.1 Metabolic factors

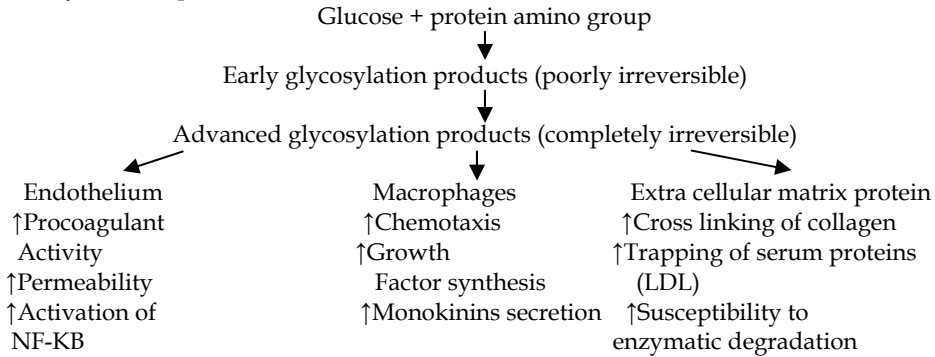
Hyperglycemia is the common feature in the two etiologic types of diabetes². Hyperglycemia influences the development of complication of diabetes through the following metabolic pathways.

a. Polyol pathway:

Glucose → Sorbitol → accumulation in nerves, retina, kidneys.

Hyperglycemia results in increased levels of sorbitol in the cell, which acts like an osmolyte a competitive inhibitor of myoinositol uptake. This preferential shunting of glucose through the sorbitol pathway results in decreased mitochondrial pyruvate utilization and decreased energy production. This process is termed "Hyperglycemia induced pseudohypoxia."

b. Glycation of proteins:



3.2 Vascular changes

Involvement of the blood vessels by atherosclerosis leading to ischaemia is a significant factor in diabetic foot. Lower extremity peripheral vascular disease (PVD) is the most common factor associated with limb ulceration gangrene, impaired wound healing and ultimately amputation².

It mainly occurs in

- blood flow changes
- occlusive changes
- micro angiopathy
- hematological changes

Blood flow changes: There is marked change in the flow of blood in peripheral vessels. The microcirculation is regulated by neural factors, local reflexes and vasoactive mediators. The initial haemodynamic changes will be increased flow and pressure of capillary blood⁹. As the disease progresses, autoregulation is lost and haemodynamic stress results. It could also be due to increased calcification of vessels or AV shunting or hyperosmolarity of blood. It is well documented by high ankle brachial ratio and also Doppler studies.

Occlusive changes: More than 50% of diabetics having the disease for more than 10 – 15 years are documented to have atherosclerotic changes⁶. It mainly affects arteries below profunda femoris and is characterized by multiple segment involvement. The tibial & peroneal arteries between the knee and the ankle are primarily affected. Dorsalis pedis artery and foot vessels are usually spared. Patients with diabetes have diminished ability to establish collateral circulation especially in arteries around knee². Atherosclerotic vascular disease is more prevalent & accelerated with diabetes mellitus.

Risk factors

- Hyper triglyceridemia (very low density lipo protein – VLDL)
- Low levels of high density lipo protein (HDL)
- Increase in cholesterol: Lecithin ratio

Pathogenesis: Enhanced non-enzymatic glycosylation of lipoprotein has been shown to impair the binding of glycosylated LDL to the LDL receptor. Glycosylated LDL enhances the formation of cholesteryl ester and accumulation of human macrophages - formation of foam cells characteristic of the early atheromatous lesion⁷.

It is also noted that, vascular smooth muscle cells exhibit increased growth on exposure to high glucose in vitro.

Endothelium

Polyol pathway	}	Proliferation ⁸
Advanced glycation products		DNA damages
Diacyl glycerol Protein kinase pathway		Matrix protein synthesis
		Permeability
		Coagulation

Blue toe syndrome which is sudden onset of pain in the toe with bluish discoloration associated with leg/thigh myalgia and a sharp demarcated gangrenous toe is seen in diabetic foot. This is due to cholesterol emboli that break off from an ulcerated atheromatous plaque in the proximal vessels. Warfarin is used in treatment.

Microangiopathy: Hyperglycemia causes thickening of basement membrane of small vessels and capillaries due to incorporation of carbohydrates into basement membrane by induction of enzymes such as glycosyl, galactosyl transferase. Williamson et al observed that basement membrane thickening in the most dependent portion of the body may be the cause of increased hydrostatic pressure.

The chemical changes in basement membrane are:

- Increased hydroxylysine and glucose disaccharide content
- Decrease in proteoglycan and Heparin sulfate
- Increase in collagen type IV
- Decrease in lysine
- Decrease in laminin

Thickening interferes with transfer of oxygen and nutrients to the tissues and delays migration of leucocytes to the area of sepsis, thereby delaying wound healing.

Haematological changes:

The haematological abnormalities are increased plasma and blood viscosity such as alteration in the plasma protein profile and disturbance in erythrocyte behavior. Erythrocytes are prone to increased aggregation and also show reduced deformability¹⁰. As glutathione metabolism is impaired in DM, the erythrocyte defenses against oxidative stress is impaired.

Haemostatic imbalances originate from acquired coagulation defects. The abnormalities of haemostatic system in DM are:

Endothelium	↓ Prostacyclin
	↓ Tissue factor production
Platelets:	↑ Hyper sensitivity to agonists
	↑ aggregation
	↓ Membrane fluidity
	↓ Platelet volume

Coagulation abnormalities are:

Coagulation factors

- ↑ Fibrinogen-
- ↑ factor VII, factor VIII and
- ↑ Von willebrands factor

Coagulation inhibitors

- ↓ Antithrombin III activity
- ↓ Heparin cofactor II activity
- ↓ Thrombin - antithrombin complex levels
- ↓ Protein C levels

Fibrinolysis abnormalities

- ↑ Plasminogen activator inhibitor
- Mega karyocyte platelet system is activated in diabetes mellitus.

Signs & symptoms of diabetic foot and leg caused by vascular abnormalities

1. Intermittent claudication
2. Cold feet
3. Rest pain
4. Absent pulses
5. Dependent rubour
6. Atrophic skin changes
7. Ulceration
8. Infection
9. Gangrene
 - a. Type I patchy gangrene
 - b. Type II extensive gangrene

3.3 Neuropathy in the diabetic foot

Peripheral neuropathies are found in 55% of diabetics. The incidence of neuropathies increases with duration of disease and episodes of neuropathies increases with duration of disease and episodes of hyperglycemia. Peripheral neuropathy clearly renders the patient to unrecognized injury, which potentates the risk of bacterial invasion and infection¹¹.

Definition of diabetic neuropathy: The presently accepted definition is demonstrable (clinical or sub clinical) disorder of somatic or autonomic parts of peripheral nervous system occurring in patients with DM¹²

Signs & symptoms

1. Paraesthesia
2. Hyperaesthesia
3. Hypoaesthesia
4. Radicular pain
5. Loss of deep tendon reflexes
6. Loss of vibratory and position sense
7. Anhydrosis
8. Heavy callus formation over pressure points¹³.
9. Infection complication of trophic ulcers
10. Foot drop

11. Change in bones and joints
12. Radiographic changes
 - a. Demineralization
 - b. Osteolysis
 - c. Charcot joint

Aetiology

1. Vascular aetiology causing diabetic peripheral neuropathy¹⁴.

- Basement membrane thickening
- Endothelial swelling & proliferation
- Occlusive platelet thrombi
- Closed capillaries

Multifocal ischaemic proximal nerve lesions¹⁵.

- Epineural vessel atherosclerosis
- Decreased erythrocyte deformability

Nerve hypoxia

2. Metabolic Factors:

- Accumulation of sorbitol
- Decrease in nerve Na⁺ - K⁺ ATPase
- Alteration in protein kinase C
- Decrease in aminoacid incorporation into dorsal root ganglion.
- Decrease in incorporation of glycolipids and amino acids into myelin
- Excessive glycogen accumulation.
- Nerve hypoxia

3. Other causes could be:

- Increased nerve oedema
- Increased blood nerve permeability
- Decrease in endogenous nerve growth factor
- Insulin deficiency.

3.4 Infections

In a normal individual the flora of the lower leg and foot are restricted because of following reasons:

1. Skin temperature is much lower than optimum for many human pathogens.
2. Metabolic products of skin have antimicrobial chemical effect.
3. Acid surface of the dorsum of foot & lower leg, making survival dependent on the ability of various microbes to resist drying.
4. Thick stratum corneum

Of all the infections seen in diabetic patient, bacterial and fungal infections of the skin are most common.

Predisposing factors:

- a. Vascular insufficiency
 - b. Neuropathy.
- Resistance to infection could be due to
- a. Leukocyte mobilization.
 - b. Defective chemotaxis
 - c. Neutrophil bactericidal defects

Defect in formation of reactive oxygen metabolites¹⁶.

Arterial insufficiency

locally tissues pressure & Metabolism

Increased tissue demand for oxygen

Increased extra vascular tension &

Local production of tissue destructive enzymes (phagocytes lysosomes)

Local thrombosis and small vessel occlusion

INFECTION

Commonest organisms are: Aerobes/Anaerobes

1. Gram negative bacilli : P. Mirabilis, E. Coli, P. Aeruginosa, E. Aerogenes

2. Gram - positive bacilli: Enterococcus Spp, S. Aureus, Group B. Strepto coccus

Anaerobes:

1. Gram negative bacilli: B. Fragilis, B. Ovatus, B. Ureolyticus

2. Gram positive bacilli: P.Magnus, P. Anaerobes, C. Bifirmentans

The infections are Polymicrobial in DM



Dry gangrene

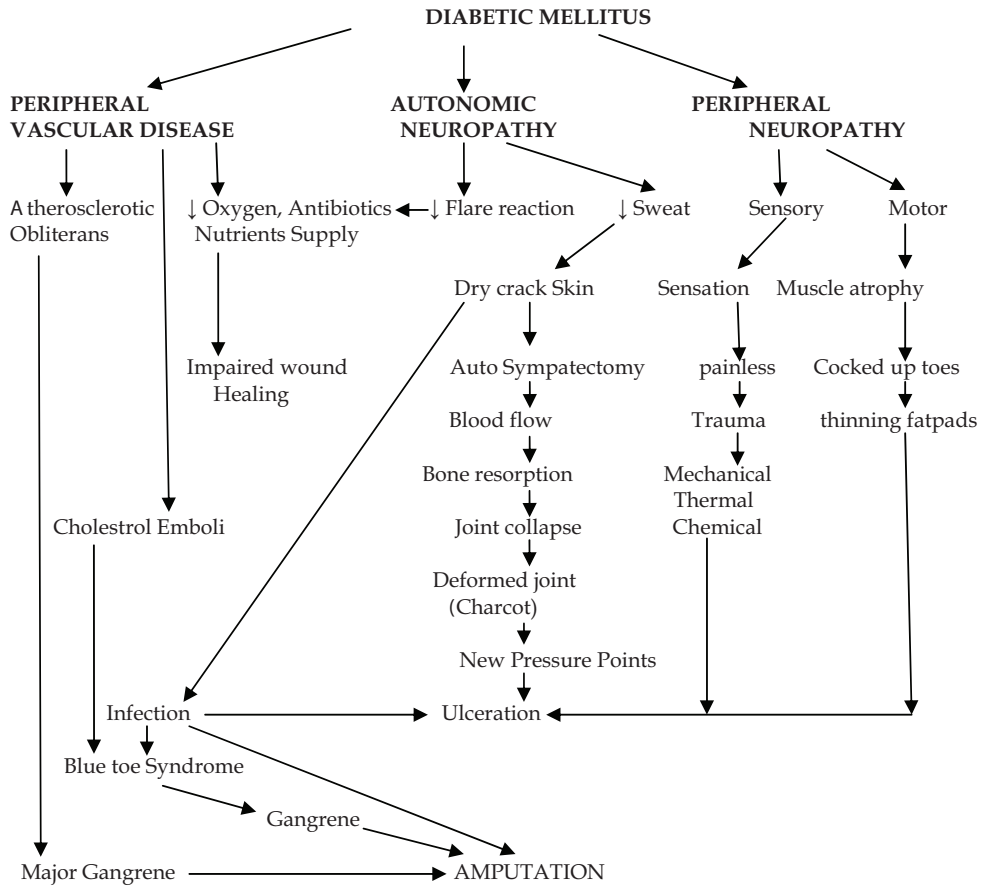


Wet gangrene



To summarise the pathogenesis, Salvapandian reviewed the different types of foot infections and their characteristics in 1982¹⁷. These infections can occur in nondiabetic as well as diabetic persons, although the presence of the diabetic state can aggravate the risks and the morbidity associated with these infections. Post-traumatic foot infections can be classified as follows.

1. **Infected blister:** This is usually secondary to improperly fitting footwear, which causes separation of the superficial layers of the epidermis from the deeper layers.
2. **Infected abrasion:** This follows the traumatic removal of the horny layer of the skin, leaving the deeper layers open to the elements.
3. **Infected ulcer:** This usually is an extension of a previous abrasion and is usually due to pressure from the outside.
4. **Puncture wounds**
5. **Infected calluses.** These are usually a result of repeated intermittent pressure due to poorly fitting footwear and /or bony prominences and foot deformities as an end result of diabetic neuropathy and oosteroarthropathy
6. **Infected corns:** These are conical wedges of keratinized tissue with the apices pointing inward. These usually occur on the heel or under metatarsal heads.



7. Infections following severe mechanical trauma such as in crush injuries or degloving injuries.
8. Infections can also follow the development of open areas in the skin such as the development of fissures. These fissures commonly occur between the toes or in the flexor creases of the toes.



Infected ulcer in a diabetic patient

Depending on the severity of the illness and the extent of tissue involvement, these infections can vary in their clinical manifestations. Chronic poorly healing ulcers may be

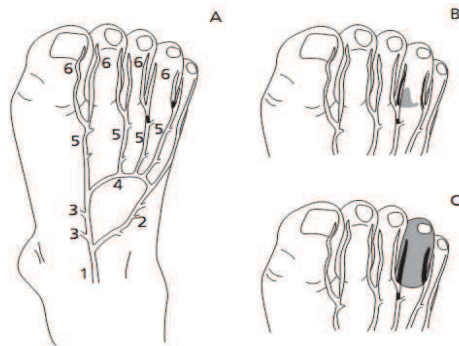
minimally symptomatic, but associated cellulites may result in fever, pain and tenderness in the involved area, and peripheral leukocytosis. The elderly diabetic patient may sometimes manifest no systemic symptoms.

Crepitant anaerobic cellulites is a disease entity that often results from mixed anaerobic and aerobic super infection of a long-standing diabetic foot ulcer. The infection gives rise to extensive gas formation that dissects underneath the skin, thus giving rise to crepitus on palpation. Patients usually demonstrate fever and leukocytosis. With appropriate management, this infection can usually be easily controlled.

Once pyogenic infections occur in the diabetic foot, they may ascend up the leg and sometimes progress to a necrotizing soft tissue infection. These infections are frequently caused by synergistic interaction of multiple bacteria, including anaerobes, aerobes, and microaerophilic bacteria. Included in these severe and life-threatening infections are synergistic necrotizing fasciitis and nonclostridial anaerobic myonecrosis (erstwhile erroneously called synergistic necrotizing cellulitis)¹⁸.

4. Diabetic gangrene and vasculature

Atherosclerotic lesions in the arteries of diabetic patients occur at sites similar to those of non diabetic individuals (such as arterial bifurcations), while advanced disease is more common in diabetic patients, affecting even collateral vessels.



The pathology of the affected arteries is similar in both those with and those without diabetes. Typical atherosclerotic lesions in diabetic patients with peripheral vascular disease include diffuse multifocal stenosis and a predilection for the tibioperoneal arteries. All tibial arteries may be occluded, with distal reconstitution of a dorsal pedal or common plantar artery. Diabetes has the greatest impact on the smaller vessels (diameter less than 5 mm) in the body. The atherosclerotic procedure starts at a younger age and progresses more rapidly in those who have diabetics than those who do not. Although non - diabetic men are affected by peripheral vascular disease much more commonly than non- diabetic women (a male- to- female ratio of 30 : 1), diabetic women are affected half as often as diabetic men.

Gangrene is characterized by the presence of cyanotic, anesthetic tissue associated with or progressing to necrosis. It occurs when the arterial blood supply falls below minimal metabolic requirements. Gangrene can be described as dry or wet, wet gangrene being dry gangrene complicated by infection.

4.1 Blue toe syndrome



Ischemic purple patches on the toes and forefoot

4.2 Critical limb ischemia

Critical leg ischemia is any condition where there is an overwhelming likelihood that the limb is at risk for amputation or significant tissue loss within 6 months. The need for revascularization is more urgent than for patients with claudication. Critical limb ischemia occurs when distal limb perfusion is impaired to the extent that oxygen delivery is insufficient to meet resting metabolic tissue demands, and it follows inadequate adaptation of the peripheral circulation to chronic ischemia (collateral recruitment and vasodilatation). According to the consensus statement on critical limb ischemia (Norgren et al., 2007), critical leg ischemia is defined as either of the following two criteria:

- a. persistently recurring ischemic rest pain requiring regular adequate analgesia for more than 2 weeks, with an ankle systolic pressure of 50 mmHg or less and/or a toe pressure of 30 mmHg or less;
- b. ulceration or gangrene of the foot or toes, with an ankle systolic pressure of 50 mmHg or below and/or a toe pressure of 30 mmHg or less. In such patients, it is important to differentiate neuropathic pain from ischemic rest pain.

Critical leg ischemia is dominated by pedal pain (except in diabetic patients, where the superficial pain sensation may be altered and they may experience only deep ischemic pain, such as calf claudication and ischemic rest pain). In most cases, the pedal pain is intolerably severe; it may respond to foot dependency, but otherwise responds only to opiates.

Critical limb ischemia is manifested by rest pain (Rutherford classification category 4) or tissue loss. Rest pain is less frequent in individuals with diabetes because of the concomitant neuropathy. The rate of progression of peripheral arterial disease in patients with claudication to critical limb ischemia is 1.4% a year; progression is more likely in patients with diabetes and in tobacco smokers.

4.3 Diabetic gangrene ('end artery' disease)

In the normal foot, major injuries and operations are well tolerated by means of the arterial circulation distal to the ankle, since the plantar and the dorsal arches, their communications and the smaller arteries are patent. In the diabetic foot, however, smaller unnamed arteries may function as 'end - arteries' due to multiple complete blockade and/or partial constrictive atherosclerotic lesions. Therefore local edema and thrombosis due to toxins produced by some bacteria (mainly staphylococci and streptococci) may cause ischemic necrosis of the tip of a toe or a part of its surface or of one or more toes, even when pulses are present in the foot arteries.

In the case of localized necrosis of the tip of a toe, removal of the gangrenous tissue, together with aggressive treatment of the infection, may lead to healing as long as the small arteries are still patent. Transluminal angioplasty or stenting of the occluded arteries will allow proper antibiotic treatment and salvage of the foot, while a gangrenous toe will be isolated by mummification (dry gangrene) without major consequences. Gangrene of the fifth toe or the hallux is due to more extended atherosclerotic disease and will probably lead to toe amputation or disarticulation.

4.4 Gangrene due to abscess of the plantar space

In a plantar space abscess, edema can obliterate the plantar arterial arch and its branches, leading to ischemia and necrosis of the middle toes, together with the central plantar space. The fifth toe and the hallux receive branches through the lateral and medial plantar spaces, respectively, and may survive central plantar space abscesses

4.5 Wet gangrene

A moist appearance, gross swelling and blistering characterize wet gangrene. Cellulitis (erythema) and the typical signs of inflammation are evident. Pus may be present. The patient may or may not be febrile, and pain is present unless there is loss of pain sensation due to diabetic neuropathy. Small vesicles or yellow, bluish or black bullae may form, and eventually a black eschar covers the infected necrotic area. This is an emergency occurring in patients with severe ischemia who sustain an unrecognized trauma to their toe or foot. Urgent debridement of all affected tissues and the use of antibiotics often results in healing if sufficient viable tissue is present to maintain a functional foot, together with adequate circulation. If wet gangrene involves an extensive part of the foot, urgent guillotine amputation at a level proximal enough to encompass the necrosis and gross infection may be life - saving. At the same time, bypass surgery or a percutaneous transluminal angioplasty needs to be performed, if feasible. Saline gauze dressings, changed every 8 hours work well for open amputations. Revision to a below -knee amputation may be considered 3 - 5 days later. Wet gangrene is the most common cause of foot amputation in persons with diabetes. It often occurs in patients with severe peripheral vascular disease after infection. Dry gangrene may be infected and progress to wet gangrene.

Patients with dry gangrene who are awaiting a surgical procedure need education about meticulous foot care. It is extremely important for patients to avoid wet dressings and debriding agents, as their use may convert a localized dry gangrene to limb - threatening wet gangrene. Proper footwear is crucial to avoid further injury to the ischemic tissue.

4.6 Dry gangrene

Dry gangrene is characterized by its hard, dry and wrinkled dark brown or black texture; it usually occurs on the distal aspects of the toes often with a clear demarcation between viable and necrotic tissue. Once demarcation has occurred, the involved toes may be allowed to auto amputate. However, this process is long (several months) and disturbing. In addition, many patients do not have an adequate circulation to heal a distal amputation. For these reasons, it is common practice to evaluate the arteries angiographically and perform a bypass or a percutaneous transluminal angioplasty with concomitant limited distal amputation, in order to improve the chance of wound healing. In the case of extended gangrene, amputation at a higher level is unavoidable.

5. Lower Extremity Arterial Disease (LEAD)

The incidence and prevalence of LEAD increase with age in both diabetic and nondiabetic subjects and, in those with diabetes, increase with duration of diabetes. Many elderly diabetic persons have LEAD at the time of diabetes diagnosis. Diabetes is an important risk factor for LEAD. Hypertension, smoking, and hyperlipidemia, which are frequently present in patients with diabetes, contribute additional risk for vascular disease. LEAD in diabetes is compounded by the presence of peripheral neuropathy and by susceptibility to infection. These confounding factors in diabetic patients contribute to progression of LEAD to foot ulcerations, gangrene, and ultimately to amputation of part of the affected extremity. Prevention is an important component of LEAD management. By the time LEAD becomes clinically manifest, it may be too late to salvage an extremity, or it may require more costly resources to improve the circulatory health of the extremity.

LEAD manifests itself by decreased arterial perfusion to the lower extremities. This decreased perfusion results in diminution or absence of peripheral pulses and may lead to intermittent claudication (pain on walking, relieved promptly by rest), proneness to infection, ulcerations, poor healing of sores and ulcers, gangrene, and ultimately to amputation. Intermittent claudication is indicative of clinical occlusive LEAD.

Palpation of peripheral pulses has been used as a clinical tool to assess occlusive LEAD in diabetic and nondiabetic patients, particularly when intermittent claudication is present. However, it is sometimes difficult to interpret the significance of diminished peripheral pulses when symptoms are not present. Ambient temperature, anatomic variation, and expertise in palpating peripheral pulses may contribute to variation in the clinical examination. Absence of pulses remains a significant clinical finding. Absent posterior tibial, popliteal, or femoral pulses with or without bruits that persist on repeated examination are clinically significant and indicate significant occlusive LEAD whether intermittent claudication is present or not.

Angiography remains the gold standard for identifying occlusive LEAD and the areas of occlusion in the arterial system. Patients being considered for amputation because of occlusive LEAD should have angiography performed to determine whether revascularization may be effective in salvaging the limb or in lowering the level of amputation.

Diabetic vasculature

Two types of vascular disease are seen in patients with diabetes: a **non occlusive micro circulatory dysfunction** involving the capillaries and arterioles of the kidneys, retina, and peripheral nerves, and a **macroangiopathy** characterized by atherosclerotic lesions of the coronary and peripheral arterial circulation. The former is relatively unique to diabetes, whereas the latter lesions are morphologically and functionally similar in both non diabetic and diabetic patients. As it became increasingly evident that the vasculature of the foot was spared the changes noted in the more proximal vessels, measurement of digital toe pressures was initiated. Subsequent study has confirmed that toe pressures are not hampered by the coexistence of diabetes. In fact, Vincent et al. showed that toe pressure was an accurate hemodynamic indicator of total peripheral arterial obstructive disease in diabetics.

Angiography is indicated in the diabetic patients with non healing ulcers or osteomyelitis requiring endovascular and surgical planning. Almost without exception, these patients with nonhealing foot ulcers will have severe stenooclusive disease involving all three runoff vessels of the calf (anterior tibial, posterior tibial, and peroneal arteries). In this

patient population, 20% of peripheral bypass grafts will have to extend to a pedal artery. The distal anastomosis is either to the dorsalis pedis artery or the proximal common plantar artery trunk (54). Thus detailed mapping of arterial disease from the abdominal aorta to the pedal vessels is necessary. Besides palpation and bedside Doppler evaluation of pulses, the clinical examination should include a standard assessment of skin color, turgor, and temperature. Edema may be present, which thwarts a thorough physical examination of pulses. A “Dopplered” pedal pulse should be at least biphasic, to support healing. If there is any doubt about the adequacy of perfusion, then noninvasive studies should be obtained. The ankle-brachial index (ABI) may be unreliable in patients with noncompressible lower-leg vessels. In general, however, an ABI of less than 0.5 in the setting of a nonhealing wound indicates a need for vascular reconstruction. According to Colen and Musson, an ABI of 0.7 or greater is appropriate if a free flap with a distal arterial anastomosis is planned.

Gangrene

Gangrene is defined as focal or extensive necrosis of the skin and underlying tissue. However, this definition presents difficulties. There are several etiologies for gangrene, as there are for foot ulcers. One is LEAD of the large or small vessels, but infection and neuropathy may also play a role. Gangrene is better correlated with LEAD than is foot ulcer. The demonstration of clinical or subclinical LEAD is essential if gangrene is to be considered a manifestation of the progression of LEAD in the individual patient. The prevalence of gangrene is greater in selected diabetic patient populations than in the general community. However, prevalence is not a satisfactory indicator of the importance of gangrene in diabetes, compared with incidence, because of the poor survival experience of these patients and their consequent loss from the prevalent population. Risk factors for gangrene have not been adequately quantified for diabetic patients. They include LEAD, peripheral neuropathy, infection, trauma, and delayed healing.

6. Investigations

The initial assessment of PAD in patients with diabetes should begin with a thorough medical history and physical examination to help identify those patients with PAD risk factors, symptoms of claudication, rest pain, and/or functional impairment. Alternative causes of leg pain on exercise should be excluded. PAD patients present along a spectrum of severity ranging from no symptoms, intermittent claudication, rest pain, and finally to nonhealing wounds and gangrene.

Palpation of peripheral pulses should be a routine component of the physical exam and should include assessment of the femoral, popliteal, and pedal vessels. It should be noted that pulse assessment is a learned skill and has a high degree of interobserver variability, with high false-positive and false-negative rates. The dorsalis pedis pulse is reported to be absent in 8.1% of healthy individuals, and the posterior tibial pulse is absent in 2.0%. Nevertheless, the absence of both pedal pulses, when assessed by a person experienced in this technique, strongly suggests the presence of vascular disease.

The ABI is measured by placing the patient in a supine position for 5 min. Systolic blood pressure is measured in both arms, and the higher value is used as the denominator of the ABI. Systolic blood pressure is then measured in the dorsalis pedis and posterior tibial arteries by placing the cuff just above the ankle. The higher value is the numerator of the ABI in each limb.

The diagnostic criteria for Peripheral artery disease (PAD) based on the ABI are interpreted as follows:

- Normal if 0.91–1.30
- Mild obstruction if 0.70–0.90
- Moderate obstruction if 0.40–0.69
- Severe obstruction if <0.40
- Poorly compressible if >1.30

An ABI value >1.3 suggests poorly compressible arteries at the ankle level due to the presence of medial arterial calcification. This makes the diagnosis by ABI alone less reliable.

The following investigations are done for the diagnosis and treatment of diabetic foot:

1. To demonstrate the extent and severity of the disease process.
2. To screen diabetic patients for peripheral vascular insufficiency.
3. To confirm and control the intercurrent diseases interfering with the healing process.

6.1 Urine examination

- Albumin
- Sugar

6.2 Culture and sensitivity tests

Pus from infected area is cultured for microorganisms and their sensitivity to various antibiotics.

6.3 X-Ray

X-ray of the foot should be taken to rule out osteomyelitis. The sign, which suggests the presence of osteomyelitis, is destruction of bone commonly seen at metatarsophalangeal joint or in the interphalangeal joint of the great toe. Sequestrum and subperiosteal new bones formations are common. A small amount of gas in the tissues or in the abscess cavity may be seen. Large amounts of subcutaneous gas indicates the presence of a serious anaerobic infection. In severe ischaemia, there may be generalised osteoporosis in the bone of the foot.

6.4 Non-invasive evaluation

The non-invasive techniques assumed an important role in peripheral arterial ischaemic diseases. They give an accurate assessment of anatomic and physiologic vascular status

- a. **Toe pressure** They provide a highly accurate method for determining the success in the healing of an ulcer or in minor amputation. A toe pressure of 20 - 30 mm Hg below which healing is doubtful.
- b. **Duplex scanning with ultrasound analysis (doppler study)** The recorded Doppler signal is used in two ways:
 - To measure segmental systolic pressure
 - To provide flow velocity wave form patterns for analysis.

Colour Doppler scanners Colour Doppler scanners detect and display moving structures by superimposing colour onto the grey-scale image. The hue of the colour can be used to identify sites where the artery becomes narrower and the blood has to move faster to achieve the same volume flow rate.

c. **Others**

- Photoplethysmography
- Segmental pressure
- Waveform evaluation

6.5 Invasive techniques

a. Angiography

Percutaneous femoral angiography

Anatomic evaluation of the vascular supply to the leg and foot require arteriography. In young patients with vascular insufficiency diagnosis of obstruction can be made when arteriogram show severe diffuse atherosclerotic disease involving the tibial and peroneal arteries. The possibility of large vessel stenosis are occlusion superimposing on distal possibility of large vessel stenosis are occlusion superimposing on distal diabetic vascular disease is most important indication for angiography.

b. Digital subtraction angiography

The term digital subtraction angiography refers to visualization of vessels using digital fluoroscopic techniques for image enhancement.

c. Radionuclide bone scintigraphy:

- Bone scanning using technetium 99m phosphonates is useful in identifying early osteomyelitis.
- Gallium accumulates in areas of active inflammation
- Sequential gallium scan are useful in monitoring the response to treatment for chronic osteomyelitis.

d. Computed tomography

- Well suited for imaging complex articulations and numerous soft tissue structure.
- Can identify and characterize the extent of soft tissue infection.

e. Magnetic resonance imaging

- Detects and displays bone marrow alterations in osteomyelitis
- Displays the contrast between soft tissue, medullary tissue and cortex with clarity.

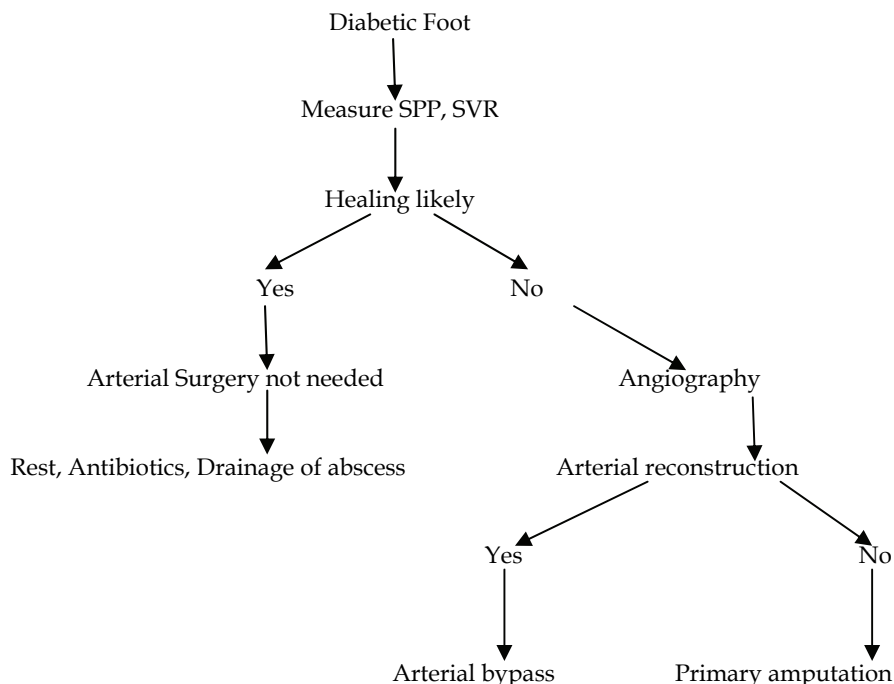
7. Prognosticating factors

Chance of Ischemic Rest Pain Ankle pressure	Unlikely	Probable	Likely
Non diabetic	More than 55	35 - 55	Less than 35
Diabetic	More than 80	55-80	Less than 55

Prediction of Healing of Ulcer Ankle pressure	Likely	Probable	Unlikely
Non diabetic	More than 65	55 - 65	Less than 55
Diabetic	More than 90	80 - 90	Less than 80

Chance of below knee Amputation Healing Diabetics	Likely	Probable	Unlikely
Calf pressure	More than 65	More than 65	Less than 65
Ankle pressure	More than 30	More than 30	Less than 30

CHART FOR MANAGEMENT OF DIABETIC FOOT



8. Management of diabetic gangrene

The management of diabetic gangrene has to be individualized. Factors that have to be considered include manifestations of sepsis, the extent of tissue necrosis and gangrene, the adequacy of the vascularity to the involved limb, the extent and severity of the soft tissue infection, the presence and extent of bone involvement, the severity of the peripheral neuropathy, the presence and severity of foot deformity, and the metabolic control of the diabetic state. If the diabetes is not adequately controlled, insulin therapy should be initiated. Surgical intervention is of paramount importance in most of these infections. Some patients may benefit from vascular reconstruction, since patients with nonhealing or poorly healing ulcers secondary to vascular insufficiency may heal following vascular surgery.

8.1 Antimicrobial therapy

Mild infections: If there are no clinical manifestations of sepsis, mono antibiotic therapy may be instituted while awaiting culture and sensitivity reports. In the absence of necrotic tissue, foul smelling discharge & frank gangrene, it is more common to isolate single microorganisms and anaerobes are relatively uncommon¹⁹. In this, gram +ve aerobic cocci are usually dominant organisms.

Included under these: *Staphylococcus aureus*, Coagulase -ve staphylococci, Nongroup D streptococci, Enterococci

First generation Cephalosporins will cover first 2 organisms, but are inactive against remaining organisms. Ticarcillin - Clavulanate and imipenem will be adequate for most

coagulase positive and negative staphylococci. For Gram +ve organisms Ampicillin – Sulbactam will provide adequate coverage.

Severe infections: In the presence of more severe infections, especially when tissue necrosis and gangrene are present, when the infections process is rapidly progressive and / or when toxemia, hypotensive shock, and other signs of sepsis are present, more broad spectrum, antibiotic therapy is indicated. In addition to staphylococci and enterococci, anaerobes as *B. fragilis* and gram -ve aerobic bacilli *P. aeruginosa* are frequently isolated and may respond to clindamycin²⁰.

Metronidazole is excellent against Gram-negative anaerobic bacilli, but has limited activity against gram positive anaerobic and microaerophilic cocci. Imipenem, ticarcillin clavulanate and ampicillin – sulbactam all have excellent activity against almost all anaerobic bacteria²¹. There is reluctance in using amino glycosides in diabetic patients due to evidence of diabetic nephropathy in these patients and amino glycosides might worsen the nephropathy²². The choice of an antipseudomonal agent is likely to be antipseudomonal B- lactam or quinolones. With severe infections or presence of toxemia or septicemia, it may be prudent to use a combination of atleast two antimicrobial agents as preliminary empirical therapy pending knowledge of deep tissue culture & sensitivity.

8.2 Saving the diabetic foot

One of the primary goals of treating diabetes is to save the diabetic foot. This can be achieved by

1. Correction of vascular risk factors
2. Improved circulation
3. Proper treatment of diabetic foot ulcers
4. Team work
5. Patient education in foot care

CORRECTION OF VASCULAR RISK FACTORS.

Risk factors for micro vascular disease are given in table below. Certain risk factors can be controlled and hence should be.

Risk factors for micro vascular disease

Non treatable	Treatable	Miscellaneous
Genetic	Smoking	Inotropic drugs
Age	Hypertension	Beta blockers
Diabetes	Hypercholesterolemia	
Duration of diabetes	Hypertriglyceridemia	
	Hypoglycemia	

Hyperinsulinemia may lead to increased atherosclerosis. First it can induce deposition of fat into the macrophages or foam cells that part of stenotic plaque. Insulin also by growth hormone like action stimulates mitotic division and growth of smooth muscle cells from media into plaque.

IMPROVED CIRCULATION

Exercise is important in building up collaterals. Vasodilators have a very minimal role, as diabetes is not a vasospastic condition. Antiplatelet drugs like aspirin and dipyridamole can be used. The basic pathology in blood is hypercoagulability and change in rheologic properties of RBC. The ability of the RBC to change shape is lost to certain degree.

Pentoxifylline is a drug, which can increase the red cell flexibility. Thus blood flow can be increased and blood viscosity decreased.

9. Wagner's grading of foot lesions

Wagner (1983) grades lesions of diabetic foot from 0-5 by depth and extent.

Grade 0 No ulcer but high risk foot

Grade 1 Superficial ulcer (commonest site is head of 1st metatarsal).

Grade 2 Deep ulcer with no bony involvement

Grade 3 Abscess with bony involvement

Grade 4 Localised gangrene

Grade 5 Gangrene of whole foot

GRADE 0 FEET

No open lesions but is at risk foot.

A large amount of callus under a metatarsal head may act as a foreign body and lead to ulcer in an open but hidden lesion and if present should be reclassified as Grade 1.

Grade 0 feet with deformities such as intrinsic, minus, hammer or claw toes, Charcot's joint or hallux valgus need purpose designed shoes. Proper patient education plays a key role in the management of diabetic patients with Grade 0 feet.

GRADE 01 LESION

Superficial ulcer but with thickness skin loss. Usually these occur in plantar surfaces of toes of metatarsal heads. But "Kission lesion" occurs in between toes caused by over-tight shoes. This is due to repeated pressure leading to ischemia. Thus mainstay of treatment is to release pressure from ulcerated area, surrounding callus removal and ulcer debridement until healthy granulation is seen. Saline irrigation is usually enough in these relatively clean superficial ulcers. If infection is present, a wound swab should be taken and antibiotic therapy with broad-spectrum agents should be started immediately. The most important part of treatment is to relieve pressure till lesions heal.

GRADE 02 LESIONS

Ulcer is deep and often penetrates subcutaneous fat down to tendon or ligament, but without abscess or bony infection. These patients should be admitted to hospital and blood and ulcer cultures should be taken and foot X-rayed.

Culture for aerobes and anaerobes should be done. Staphylococci and bacteroides are one of the two commonest isolates. Fluocloxacillin and Metronidazole are used as blind first line therapy. Deep infected ulcer need to be debrided either in ward or under general anesthesia. After debridement, deep ulcer should be packed with Eusol and paraffin in 175 mm or 250 mm gauze wick to encourage healthy granulation tissue growth. Otherwise simple dry dressing is advised. Topical antibiotics are not useful.

GRADE 03 LESIONS

Deep infection with cellulitis or abscess formation often with underlying osteomyelitis. In management, surgery is often needed. Foot X-ray ulcer and blood cultures is a must.

Absent foot pulses, low ankle pressure and diffuse arterial disease suggest that lesion will not heal without amputation. If available Doppler studies may help to decide whether to persist with conservative treatment or proceed with local amputation. If the lesion is purely neuropathic, conservative treatment is sufficient since ulcer usually heals. Initial treatment constitutes bed rest, elevation of foot, antibiotics according to culture and sensitivity. Optimal glycaemic control is also needed. Grade 3 foot with good blood supply can often be

treatment with amputation, with surgical drainage, dressing and wound irrigation. Amputation may be needed if severe infection or progressive anaerobic infection is present.

GRADE 04 LESIONS

Treatment is same as Grade 3 lesion. Avoid pressure bearing either with special shoes or bed rest is the mainstay of treatment. When distal vascularity is adequate it is worthwhile trying conservatism. Arteriography is indicated to see whether bypass or angioplasty is indicated. If neither is possible, if there is no rest pain, then a period of conservative treatment is worthwhile. A painless black toe with dry gangrene often amputates spontaneously if left alone. In a previously mobility patient, a below knee amputation is better than above knee amputation because of better rehabilitation.

GRADE 05 LESIONS

These patients have extensive gangrene of the foot and needs urgent hospital admission, control of diabetes and infection and major amputation.

10. Buerger's disease (thromboangittis obliterans)²³

Characterized in histology by thrombosis in both arteries and veins with marked inflammatory reaction. This classic condition described by Buerger involves young men with severe ischaemia of the extremities who are addicted to cigarette smoking and often have migratory superficial phlebitis.

Definition - It is an inflammatory reaction in the arterial wall with involvement of the neighbouring vein and nerve, terminating in thromboses of the artery. It is probably presenile atherosclerosis occurring in the 3rd, 4th, and 5th decades of the life.

Incidence - more frequently in men between 20 and 40 years of age. It is uncommon in women, who constitute only 5% to 10% of all patients with Buerger's disease.

Aetiology - interaction of multiple aetiologic factors. There is striking association of this disease with **cigarette smoking**. (> 20 cigarettes per day) There may be some **hormonal influence** which suggests the sex distribution. Patients often come from **lower socio-economic groups**. A **hypercoagulable state** has been postulated. There has also been report of hyperaggregability of platelets. **Familial predisposition** has been reported. **Autonomic overactivity** has been suggested by a few pathologists, as there is also sometimes peripheral vasospasm and hyperhidrosis noticed in this condition. Recently an **autoimmune aetiology** has been postulated.

Pathology - An obvious inflammatory process features the Buerger's disease involving all layers of the vessel wall. Thrombus is noticed in the lumen of the affected artery. There are also microabscesses within the thrombus. In the late stage the affected artery becomes occluded and contracted with marked fibrotic reaction affecting all the layers of the artery e.g. the adventitia, the media and intima. This fibrotic process gradually involves the vein and adjacent nerves. The lesions in Buerger's disease are segmental and usually begin in arteries of small and medium size. Both upper and lower extremities are affected.

Clinical features. It is characterized as peripheral ischaemia, particularly if the upper extremity is involved and it there is a history of migratory superficial phlebitis.

SYMPTOMS Complain of pain at the arch of the foot (foot claudication) while walking. Pain is typical of intermittent claudication type. Intermittent claudication progresses to rest pain. Gradually postural colour changes appear followed by trophic changes, eventually ulceration and gangrene of one or more digits and finally of the entire foot or hand may take place. When rest pain develops, it is so intense that the patient cannot sleep. If the affected

limb is kept in dependent position some relief of pain may be obtained. The limbs become rubor or red on dependence and pallor on elevation.

Special Investigations: Arteriography is the most important investigation in this condition. In arteriography it is the peripheral arteries which are first involved. There is usually extensive collateral circulation surrounding the involved arteries which look like 'tree-roots' or 'spider legs'. In approximately 1/4th of cases one can find a characteristic 'cork-screw' appearance in the vicinity of the affected artery, presumably due to greatly dilated vasa vasorum of the occluded artery.

Treatment - Pain is the most important symptom of Buerger's disease which requires to be relieved. Narcotics may be necessary, but one must be careful against drug addiction.

CONSERVATIVE TREATMENT has a great role to play -

1. Stop smoking.
2. Various drugs have been tried with different degrees of success. Vasodilator drugs, anticoagulants, dextran, phenylbutazone, inositol and steroids have all been tried. More recently prostaglandin therapy (PGA-1) has been advocated to prevent platelet aggregation.

SURGICAL TREATMENT -

1. Role of sympathectomy is doubtful.
2. Arterial reconstruction is also difficult.
3. Free omental graft for revascularisation of ischaemic extremity.
4. Amputation is the only way out when gangrene occurs. The approach is conservative and lowest possible level should be chosen.

Prognosis - The risk of amputation is about 20% within 10 years after onset of symptoms. Although this varies with the use of tobacco. In a few patients who stop smoking completely, progression of the disease is greatly restricted.

11. Osteomyelitis in diabetic patients^{24,25,26}

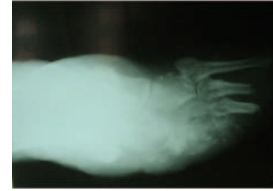
Osteomyelitis is difficult to cure, even in normal bone, because of bone's limited blood flow. An infection in bone results when bacteria are able to colonize ischemic or injured areas where the blood supply is not adequate to combat the infection with its normal defenses. As bacteria grow in this ischemic bone, they cause further bone death by vessel injury from decreases in pH, oxygen, and nutrients and increases in pressure and metabolites. When bone's blood supply is further limited by diabetic vasculitis and then by osteomyelitis, cure is more difficult. The oxygen tension of infected bone in the diabetic patient is about one-quarter that of the overlying soft tissue, which may also be very low. This ischemia is accompanied by metabolic and pH changes that decrease or prevent normal immunologic defenses and antibiotic penetrance and efficacy, and increase bacterial growth. Furthermore, the diabetic individual has decreased phagocytosis by polymorph nuclear leukocytes and decreased T-cell function. These factors make diabetic osteomyelitis a challenge to treat.

STAGES OF OSTEOMYELITIS

Stage I - infection is simple with no permanent anatomic damage. This is medullary osteomyelitis in a bone, acute septic arthritis in a joint, or cellulitis of soft tissue.

Stage II- is superficial periosteal or cortical osteomyelitis, chondrolysis, sub-acute septic remains arthritis, or ulcerated soft tissue.

Stage III- the infection is deeper but localized. It involves both the cortex and the medullary canal for osteomyelitis, bone about the joint for septic arthritis, or an abscess in soft tissue.



Stage IV- infection is diffuse, diffuse osteomyelitis (nonunion), end stage septic arthritis (unstable joint), or a permeating necrotizing infection (gas gangrene, necrotizing fasciitis)

Treatment Goals There are three possible treatment goals for diabetic osteomyelitis:

ARREST: “Arresting” osteomyelitis, means to debride the infection to the subthreshold level of bacteria so local tissue and antibiotics can heal the wound. Unfortunately, this is difficult for diabetic patients because of rapidly progressing ischemia.

SUPPRESSION: Suppressive therapy requires the highest amount of patient compliance and physician clinical time. An open wound is debrided in the clinic. Local wound care is done at home, and suppressive antibiotics are used to control cellulitis or progression of infection. Suppressive antibiotics are used to control cellulitis or progression of infection.

AMPUTATIONS: The team consists of a vascular surgeon, an orthopedic surgeon, and a physiotherapist and rehabilitation expert.

12. Determination of the level of amputation

Level of amputation is determined by the site at which wound healing will occur easily and leads to a residual limb which can be functionally useful. Unfortunately in diabetic patients, occlusive vascular disease leading to diabetic foot is often bilateral. That means 30-40% of such people will require amputation of the opposite limb within 2-3 years.

Many clinical signs suggest level of amputation like skin changes, vascular pulsation, and peripheral neuropathy and rest pain.

It is found that 70 mm arterial pulse at desired amputation level or a leg to arm pressure ratio more than or equal to 0.45 was found to be satisfactory and statistically valid in 80-90% patients. Occasionally patients with arterial calcification and inelastic vessel walls show abnormally high blood pressure. But waveform evaluation detects the problem. Final decision regarding level of amputation is taken as late as putting the skin incision. **SURGICAL TECHNIQUE** The gangrenous foot or leg is covered with a plastic bag or drape. Remainder of exposed limb is thoroughly cleaned with 10-minute surgical wash followed by povidone iodine solution.

12.1 Amputation of toes

- Amputation of terminal phalanx of great toe

For a functionally useful stump it is important to preserve the base of terminal phalanx

- Amputation through proximal phalanx of great toe

Not more than the base of phalanx should be therefore preserved.

- Amputation of great toe at its base

12.2 Disarticulation of the metatarsophalangeal joints

- Disarticulations of lateral four toes: Racquet approach is employed.
- **Amputation of all other toes:** Toes are disarticulated at the metatarsophalangeal joint

12.3 Amputation of foot

- **Transmetatarsal amputations** This amputation is undertaken using a long posterior flap, which extend to a level just proximal to the flexion crease at the base of toes.
- **Tarsometatarsal amputation (Lisfrank level)** This is performed through the tarsometatarsal joints and usually results in good partial amputations.
- **Midtarsal amputation (Chopart amputation)** It is a disarticulation between the os calcis and cuboid bones and talus and navicular bones and is seldom used.
- **Syme's amputation** The tibia and fibula are divided at or immediately above the level of ankle joint. The ends are covered with a single flap obtained from skin of heel.
- **Modified syme's amputation** this modification has nothing to commend and hence not widely approved.

12.4 Below knee amputation

Amputation at the below knee level through middle 3rd of leg is the operation of choice when it is not possible to conserve the foot and heel. Ideal length of tibial stump is 14 cm.

12.5 Above knee amputation

Patient can be fitted with preparatory lower limb prosthesis approximately 3-4 weeks after operation depending on healing of wound. Definitive prosthesis is usually put after 2-4 months.

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Gangrene is the term used to describe the necrosis or death of soft tissue due to obstructed circulation, usually followed by decomposition and putrefaction, a serious, potentially fatal complication. The presented book discusses different aspects of this condition, such as etiology, predisposing factors, demography, pathologic anatomy and mechanisms of development, molecular biology, immunology, microbiology and more. A variety of management strategies, including pharmacological treatment options, surgical and non-surgical solutions and auxiliary methods, are also extensively discussed in the book's chapters. The purpose of the book is not only to provide a reader with an updated information on the discussed problem, but also to give an opportunity for expert opinions exchange and experience sharing. The book contains a collection of 13 articles, contributed by experts, who have conducted a research in the selected area, and also possesses a vast experience in practical management of gangrene and necrosis of different locations.

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